

REMARKS

Reexamination and reconsideration in light of the foregoing amendments and following remarks are respectfully requested.

Claims 1-24 are pending in the application. Claims 1-15 and 20-24 are under consideration, and Claims 16-19 have been withdrawn from further consideration. Claims 6, 15 and 20 are currently amended.

It is noted that the counterpart EPO application (EP 03768629.2) has been allowed as of July 23, 2007. Allowed claims 1-15 of that application correspond to Claims 1-15 in the instant U.S. Application.

For the sake of clarity, each objection/rejection is addressed by making reference to the paragraph numbering found in the Office Action.

Paragraphs 1-6 are hereby acknowledged.

I. PARA 7. SPECIFICATION OBJECTIONS

At **Para 7(a)** the disclosure has been objected insofar as it *"refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified."*

Applicants have reviewed the specification and deleted the website address on page 38, ¶ [0102]. Applicants note that the website address is not necessary to the specification as the Fischer's Exact Test is well known and routinely practiced in the art. Because the specification as amended complies with M.P.E.P. 608.01, withdrawal of the instant objection is respectfully requested.

At **Para 7(b)** the disclosure *"is objected to because the use of improperly demarcated trademarks has been noted in this application."*

Applicants have reviewed the specification and have corrected the same by including appropriate symbols to indicate their proprietary nature. Specifically, Applicants have amended ¶¶ [0085], [0087] and [0098]. Withdrawal of the instant objection is kindly solicited.

At **Para 7(c)**, *"the specification is objected to as failing to provide proper antecedent basis for [...] the methods of claims 1-15."*

Applicants respectfully disagree, and kindly draw the Examiner's attention to ¶ [0010] of the specification. Paragraph [0010] recites the entirety of independent claim 1 *verbatim*.

Antecedent basis for method claims 1-15 can be found throughout the specification, see e.g., ¶¶ [0010], [0054]-[0101]. Accordingly, Applicants respectfully request that the objection be withdrawn.

As to **Para 7(d)**, Applicants have sought to correct much regretted typographical errors and grammatical errors. Specifically, Applicants have corrected ¶¶ [0009], [0054] and [0070].

None of the amendments hereunder add new matter. Withdrawal of the objections is respectfully requested.

II. PARA 8. CLAIMS OBJECTIONS

At Para 8(a),

"[c]laim 6 is objected to because claim 1 requires step (a) to be examined in addition to one or more of steps (b)-(e), but claim 6 recites that the expression of one or more of (a)-(e) is examined. Therefore, claim 6 should recite that (a) is examined and one or more of (b)-(e) are examined before reciting the agent used in examining one or more of them."

Applicants have amended Claim 6 in order to recite that the expression of (a) and one or more of (b)-(e) is examined using an antibody. This Amendment does not add new matter and, accordingly, Applicants respectfully request that the objection be withdrawn.

At Para 8(a), *"[c]laim 7-10 are objected to as not necessarily further limiting the methods of claim 6 and claim 1."*

Applicants respectfully disagree. Claim 6 limits Claim 1 by requiring that the expression of (a) and one or more of (b)-(e) is examined using any *antibody*. Claims 7-10 further limit Claims 6 and 1 by requiring that the antibody used be an antibody that either: binds to an epitope comprising the phosphorylated serine at position 235 in SEQ ID NO: 1; is specific for EGFR or is specific for PTEN; binds an epitope comprising a phosphorylated serine residue at position 473 in SEQ ID NO: 4; or binds an epitope comprising a phosphorylated threonine residue at position 202 or a phosphorylated tyrosine residue at position 204 in SEQ ID NO: 8 (See claims 7-10, respectively). Since Claims 7-10 require the use of certain antibodies and not just *any antibody* (as does claim 6), claims 7-10 do properly limit independent Claims 1 and 6. Accordingly, Applicants respectfully request that the objection be withdrawn.

At Para 8(c), *"Claim 15 is objected to for reciting "is identified a tumor."*

Applicants have amended Claim 15 to properly recite "*is identified as a tumor.*" This amendment does not add new matter and, accordingly, Applicants respectfully request that the objection be withdrawn.

At **Para 8(d)**, "[c]laim 20 is objected to for the typographical error "*EFGR.*"

Applicants have amended Claim 20 to properly recite "*EGFR.*" This amendment does not add new matter and, accordingly withdrawal of the objection is kindly requested.

III. THE AMENDED CLAIMS COMPLY WITH 35 U.S.C. § 112, 2ND PARAGRAPH

At **Para 10 (a)-(d)** Claims 1-15 have been rejected under 35 U.S.C. § 112, second paragraph. Each rejection is taken up separately in the following paragraphs.

With respect to **Para 10(a)**, relating to the expression "*likely to respond,*" Applicants aver that the expression is commonly used and understood in the field. The term is said to be a relative term (see page 5 line 7), which is therefore found to be indefinite.

When a cell is said to be likely to respond, one of skill will surmise that it means that such cell is more likely than not to respond. The term conveys the notion that each cell is unique and while nothing is ever certain, the methods of the invention will assess whether a given cell is more likely than not to respond to a given modality. The value of the methods are best understood in reference to similar studies also casting outcomes as to their relative significance rather than in absolute terms. To exemplify, please consider Mellinghoff et al. (N. Engl. J. Med. 353(19):2012-2024 (2005) relating to molecular determinants of the response of glioblastoma to EGFR kinase inhibitors, which also uses the same expression "likely to respond" in the context of predictive markers. In the context of the instant Application, likely to respond is discussed in terms of growth inhibition or any other medical standard indication of drug efficacy.

Accordingly, the reconsideration and withdrawal of the rejections of the Claims is respectfully requested.

At **Para 10(b)**,

"[c]laims 1-15 are rejected under 35 U.S.C. 112, second paragraph as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. [...] However, the claim also refers to correlations with potential treatments for a mammalian glioma tumor that appear to omit steps of determining either increased or decreased expression of PTEN, increased expression and or activity of EGFR [...]."

Applicants respectfully traverse. The Claims recite the step of ascertaining (a) the level of expression of PTEN, which inherently leads to establish whether PTEN expression is increased or decreased; (b) the presence of any of the listed markers. Ascertaining the presence of any one of the markers recited in the Claims is effected by IHC scoring, as illustrated by representative examples, (see e.g., ¶ [109] relating to the EGFR, and ¶ [110] relating to pAKT, pS6, and pERK). Per force, one would also learn whether there is an increase or a decrease in expression or phosphorylation of a given analyte as a result of the same step as recited. Accordingly, it is submitted that no essential step has been omitted and that therefore there is no gap.

Reconsideration and withdrawal of the rejections of Claims 1-15 are respectfully requested.

Para 10(c) sets forth a form rejection in relation to the recitation of the SEQ ID NOs appearing in the Claims as pending. Applicants aver the Claims are in compliance with the 37 C.F.R. (in particular C.F.R. § 1.821). Reconsideration and withdrawal of these rejections is kindly requested.

Para 10(d) contains a rejection based on the recitation of the term "is determined" appearing in Claims 2 and 3. Applicants submit that the Claims are directed to the detection of a phosphorylated peptide (rather than "a peptide" without the characterization of it being phosphorylated) means that one is determining whether a given peptide in its phosphorylated state is detected. Reconsideration and withdrawal of these rejections is kindly requested.

IV. THE AMENDED CLAIMS COMPLY WITH THE ENABLEMENT REQUIREMENT

At **Para 12** (page 9, line 21 *et seq.*), Claims 1-15 have been rejected as failing to comply with 35 U.S.C. §112 1st Para. The rejections are based on the incorrect finding that,

"the use of the claimed invention has not been exemplified; and moreover, there is no guidance or exemplification [...] that provides a predictive correlation linking levels of expression of PTEN polypeptide, EGFR polypeptide, phospho-S6 ribosomal polypeptide, phospho-ERK polypeptide, and phospho-AKT alone or in any specific combination before, and in the absence of, treatment with specific treatment regimen. Therefore, the specification does not enable methods that will identify a glioma tumor as likely to respond to mTOR and EGFR polypeptide inhibitor."

Applicants have provided data substantiating the significance of the relations between the expression of the various moieties according to Claims 1-15 by correlating the levels of expression of each such moiety by immunohistochemical staining ("IHC") in various experiments including those found in the Examples. In Examples 3-6, data corresponding to representative samples testing is provided. The prognostic relevance of such data in relation to various events is analyzed

for example in Example 7, which makes reference to Fig. 3 showing such a correlation in tumor patients. It is noted that data showing the correlation according the pending Claims 1-15 is provided for as many as 45 glioblastoma patients.

Accordingly, it is respectfully submitted that, the specification does enable methods that will identify a glioma tumor as likely to respond to mTOR and EGFR polypeptide inhibitor.

At **Para 12** (page 9, line 28 *et seq.*), Claims 1-15 have been rejected on the basis that,

'[...] since the specification only provides guidance or exemplification that identifies a glioblastoma multiforme response to a mTOR inhibitor is shown to decrease the phospho-S6 ribosomal polypeptide present in a tumor sample as compared to a sample from the same patient before treatment, one of skill in the art would be subject to undue experimentation to determine if any other expression pattern before treatment or change in expression pattern after treatment of these biomarkers could predictably identify a glioma as likely to respond or responsive to a mTOR polypeptide inhibitor or EGFR polypeptide inhibitor.' (underline added for emphasis)

As best understood, the argument is that enablement has not been satisfied because there might be other markers which may provide alternative suitable responsiveness predictors for an *mTOR polypeptide inhibitor or an EGFR polypeptide inhibitor*. Applicants are seeking to obtain claims directed to methods based on those predictors Applicants have actually identified, which provide the basis of the claims. In other words, Applicants have devised a suitable solution to a known problem, *i.e.*, how to ascertain tumor responsiveness by looking at certain markers. Applicants are not aware of a duty to provide any and all possible markers which may have similar applicability.

At **Para 12** (page 10, line 10 *et seq.*), Claims 1-15 have been rejected on the basis that,

"[...] the specification is silent as to the PTEN status in the glioblastoma multiforme tumors of the patients that were shown to be responsive, or not, to rapamycin treatment in Figure 3; yet the claimed process necessarily involves the analysis of the likely responsiveness of the glioma cells to the drug (e.g., rapamycin), which depends upon a correlation between the level of one or more markers in the cells and the presence, absence, or insufficiency of PTEN. These correlations are not established by the data presented in Figure 3."

Similarly, in the paragraphs spanning pages 10 and 11, it is argued in relevant parts that,

"research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials."

On the same vein, it is also argued that,

"[...] it is apparent that one cannot reliably and accurately predict whether the claimed process can be used effectively to determine the likelihood that glioma is, or is not, responsive to any given inhibitor of mTOR or EGFR; and because the use of the invention has not been exemplified, there is no factual evidence of record suggesting otherwise."

The Examiner is reminded that the evidence required to satisfy enablement is not tantamount to the evidence required for FDA regulatory approval entailing full fledged clinical trials. Applicants aver that the application as filed provide legally sufficient evidence to satisfy the enablement requirement as discussed in the following paragraphs.

The Examiner is directed to Example 8 providing a correlation with Ki-67 expression. The correlation between Ki-67 expression and tumor growth and ultimately patient outcome is well established in the field (see, e.g., *J. Neuroncol.* 55(3):195-204 (2001) establishing the correlation from data derived from 32 patients).

Similarly, Example 7 provides a correlation between pERK and time to tumor progression and between mTOR/pFKHR/pS6 signature and time to progression and overall survival.

Hence, Applicants submit that data provided provides a legally sufficient correlation between the activation of well established downstream pathways and patient outcomes.

For these reasons, reconsideration and withdrawal of the instant rejections is kindly requested.

V. THE AMENDED CLAIMS ARE NOVEL

At **Para 13**, Claims 1-11, and 13-15 have been found to be anticipated by Neshat *et al.*, *Proc. Natl. Acad. Sci.* 98(18):10314-10319 (2001) as evidenced by Sharma *et al.* *J. Biosci.* 11:423-433 (1987).

Neshat *et al.* provides data suggesting that (a) PTEN null cell lines have an increased mTOR –dependent S6 kinase activity; and (b) that PTEN null cell lines have enhanced sensitivity to mTOR inhibition. Neshat *et al.* does not however go beyond this correlation to arrive to a method according to Claim 1 which contemplates a test relying on a number of alternative parameters (other than PTEN expression and the presence of phosphorylated S6 ribosomal polypeptide). Neshat *et al.* does not teach every element of Claim 1 from which Claims 2-11 directly or indirectly depend. Claim 1 relates to a method for identifying a glioma tumor that is likely to respond, or is responsive to an EGFR polypeptide inhibitor or an mTOR polypeptide inhibitor, by ascertaining (a) the expression of PTEN polypeptide and the presence of at least one of, (i) phosphorylated S6 ribosomal polypeptide; (ii) EGFR polypeptide; (iii) phosphorylated AKT polypeptide; and (iv) phosphorylated ERK polypeptide. Because Neshat *et al.* does not contemplate the method of Claim 1 nor the methods found in the claims depending from Claim 1, it does not enable any of the methods according to the invention. Sharma *et al.* does not cure the deficiencies of Neshat *et al.*

Accordingly, neither reference anticipate the invention under controlling U.S. legal standards. For these reasons, reconsideration and withdrawal of the rejection of Claims 1-11 and 13-15 is respectfully requested.

VI. THE AMENDED CLAIMS ARE NON-OBVIOUS

With respect to **Para 16**, the Applicants aver that the inventions set forth in the instant Application were commonly owned at all pertinent times.

At **Para 17**, Claims 1 and 12 are rejected over Neshat *et al.* (*supra*) as evidenced by Strik *et al.*, Cancer 91(5):1013-1019 (2001). As discussed above in conjunction with the novelty rejections of the same claims, Neshat *et al.* provides data suggesting that (a) PTEN null cell lines have an increased mTOR –dependent S6 kinase activity; and (b) that PTEN null cell lines have enhanced sensitivity to mTOR inhibition. Neshat *et al.* does not however go beyond this single correlation. Neshat *et al.* findings however, do not lead Neshat *et al.* to suggest a responsiveness method according to the invention. The Office Action merely asserts that it would have been obvious to arrive to such a method even in the absence of an explicit teaching or suggestion to do so. Neshat *et al.* is deficient in several ways as it does not teach or suggest (a) a method to assess a cell responsiveness; (b) a method that correlates the expression of PTEN with phosphorylated S6, EGFR polypeptide, phosphorylated AKT polypeptide, or phosphorylated ERK polypeptide; and (c) a method suitable to assess a cell responsiveness to an EGFR inhibitor. Strik *et al.* does not cure the deficiencies of Neshat *et al.*

Applicants submit that the assertion that the invention is obvious fails to provide a basis upon which (i) one of skill in the art would be motivated to combine the various elements according to the invention; and (ii) one of skill would have a reasonable expectation of success without the benefit of the teachings found in Applicants' disclosure.

Accordingly, neither reference, alone or in combination, renders the invention obvious. For these reasons, reconsideration and withdrawal of the rejections of Claims 1-11 is respectfully requested.

At **Para 18**, Claims 20-24 are rejected over Neshat *et al.* (*supra*) in view of Monia *et al.* U.S. Patent No. 6,020,199.

Neshat *et al.* is asserted for the same propositions as set forth in conjunction with the previous set of rejections. Applicants wish to make reference to their responsive arguments above.

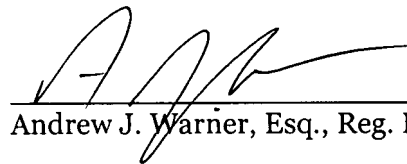
The '199 Patent is directed *inter alia* to antisense oligonucleotides PTEN antibody and secondary antibodies to be combined in a kit for the detection of PTEN. The '199 Patent does not contemplate kits including each and every analyte contemplated according to the invention. Accordingly, reconsideration and withdrawal of these rejections is respectfully requested.

VII. CONCLUSION

A Petition for a three (3) month extension of time under 37 C.F.R. § 1.136(a) is enclosed herewith. The Commissioner is hereby authorized to charge the required five hundred and ten dollar (\$510.00) fee (small entity) pursuant to 37 C.F.R. § 1.17(a)(3), along with any other fees that may be due, to Deposit Account No. 50-1774, Ref. No. CST-212. The Examiner is respectfully requested to treat any concurrent or future reply, requiring a petition for an extension of time for its timely submission, as incorporating a petition of extension of time for the appropriate length of time pursuant to 37 C.F.R. § 1.136(a)(3). Such authorization to charge all required fees under 37 C.F.R. § 1.17 or all required extensions of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission.

On the basis of the foregoing remarks and amendments, Applicants respectfully submit that the claims are in condition for allowance. Reconsideration and withdrawal of the outstanding objections and rejections is respectfully requested, and early and favorable allowance of these claims is earnestly solicited. If there are any questions regarding these amendments and remarks, the Examiner is invited to contact the undersigned attorney at the number provided below, or Simona A. Levi-Minzi (Reg. No. 43,750) at the 978.867.2311.

Respectfully submitted,
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